Pharmacokinetic Evaluation of Anticonvulsants in a Patient with Porphyria

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The aim of this study was to establish the appropriate regimen of anticonvulsants for a female patient with porphyria by pharmacokinetic evaluation of the influence of anticonvulsants on porphyria. The pharmacokinetics of phenytoin, carbamazepine, clonazepam, and clobazam were estimated by the Bayesian method. The urinary 6β-hydroxycortisol/cortisol (6β-OHF/F) ratio was also evaluated as an index of hepatic CYP3A4 induction.

The phenytoin concentrations in the toxic area fitted the predicted value for CYP2C9 *1/*3 better than that for CYP2C9 *1/*1 (her genotype). The concomitant phenytoin altered the clearance of carbamazepine considerably. The clearances of clonazepam and clobazam were not altered, although hepatic CYP3A4 induction was implied from the value of the urinary 6β-OHF/F ratio.

From the pharmacokinetic evaluations, the following were concluded: (1) phenytoin was not the proper medication for this patient, (2) carbamazepine can be used safely within a relatively small dose, 500 mg/day, (3) the combination of clonazepam and carbamazepine can be used, and (4) a concomitant small dose of clobazam with carbamazepine can also be used.

Key words: anticonvulsant, porphyria, cytochrome P450, Bayesian method, urinary 6β-hydroxycortisol/cortisol ratio

Introduction

Although many anticonvulsants are known to deteriorate porphyria, some patients with porphyria have seizures and require anticonvulsant therapy. Part of the deteriorating mechanism has been conjectured to cause an imbalance of heme protein biosynthesis, which is due to the induction of cytochrome P450 (CYP) by anticonvulsants. We previously demonstrated that the measurement of the human urinary 6β-hydroxycortisol/cortisol (6β-OHF/F) ratio is a useful indicator of safe medication in a patient with hereditary coproporphyria. The previous results implied that hepatic CYP induction was profoundly related to her condition of porphyria.

In the present paper, the pharmacokinetic parameters of the anticonvulsants used in the patient during two hospitalizations (phenytoin, carbamazepine, clonazepam, and clobazam) were retrospectively evaluated by the Bayesian method. We established the effective and safe dose of anticonvulsants for her seizures based on the alteration of the estimated pharmacokinetic parameters and the measurement of the urinary 6β-OHF/F ratio.

Case

A female in her twenties was diagnosed with rare dual porphyria involving partial δ-aminolevulinate dehydratase deficiency with epilepsy. She had been treated with sodium valproate, phenytoin and carbamazepine when she was admitted to our hospital on June 24, 1998. Sodium valproate was discontinued because of abdominal side effects. For
better control of the epilepsy, phenytoin was increased from 100 to 125 mg/day and carbamazepine was gradually increased from 800 to 1200 mg/day. However, her condition deteriorated, and the serum concentrations of phenytoin were within the toxic range. The frequency of her seizures decreased eventually by discontinuing phenytoin, gradually reducing carbamazepine, and adding clonazepam. She was discharged from our hospital after four months.

She was re-hospitalized 2 years later (March 22, 2001) for reevaluation of the medication for epilepsy. She had been treated with carbamazepine, clobazam, and zonisamide. Zonisamide was discontinued. The clobazam dose, 15 mg/day, was not changed. The carbamazepine dose was gradually increased from 450 to 500 mg/day. The frequency of her seizures decreased 2 weeks after receiving modified treatment. The urinary 6β-OHF/F ratio gathered over 24 hours was measured and compared with the value from before she left our hospital the first time1).

Methods

The patient’s genotype of the metabolic enzymes of phenytoin had been judged to be CYP2C9*1/*1 and CYP2C19*1/*21). The pharmacokinetic parameters of phenytoin were estimated from serum phenytoin concentrations in the toxic area, with the use of subpopulation parameters of CYP2C9*1/*1 and CYP2C9*1/*34). The typical predicted dose of phenytoin was calculated from equation (1) (below), based on these estimated parameters. The percentage of deviation between the predicted dose and the administered dose was calculated from equation (2) (below).

Each alteration of carbamazepine and clonazepam clearance was estimated to evaluate the pharmacokinetic influence of these agents on porphyria. In the second hospitalization, the alteration of carbamazepine and clobazam clearances was estimated. The alteration of the N-desmethylclobazam/clobazam ratio was also evaluated, because clobazam is metabolized to N-desmethylclobazam by CYP3A4. The original data used for this study were obtained as described previously1).

Her pharmacokinetic parameters of anticonvulsants were estimated by the software PEDA (parameter estimation and dosage adjustment)3) incorporating the Bayesian method, using the population pharmacokinetic parameters described in the literature4–8). The phenytoin dose was calculated by the following equation from the observed concentration of phenytoin:

\[
Dose_{\text{pre}} = \frac{V_{\text{max}}C_{\text{ss}}}{(K_m + C_{\text{ss}})}
\]

where \(V_{\text{max}}\), \(K_m\), \(Dose_{\text{pre}}\), and \(C_{\text{ss}}\) are the maximal elimination rate of the Michaelis-Menten equation (mg/day), the Michaelis-Menten constant (μg/mL), the serum concentration of phenytoin at a steady state (μg/mL), and the predicted dose (mg/day), respectively. The deviation between the dose predicted from equation (1) and the actual dose was calculated by the following equation:

\[
\text{Dev} = \frac{(Dose_{\text{act}} - Dose_{\text{pre}})}{Dose_{\text{act}}}
\]

where \(Dose_{\text{act}}\), \(Dose_{\text{pre}}\), and \(Dose_{\text{act}}\) are the deviation, the actual dose, and the predicted dose, respectively. The plasma concentrations of carbamazepine, clobazepam, and clonazepam were calculated by the following equations:

\[
C = \frac{D}{V_d} \left(\frac{K_a - K_e}{(K_a - K_e) \cdot \left(\exp(-K_{et}) - \exp(-K_{st})\right)}\right)
\]

\[
C_{\text{ss}} = \frac{D}{CL}
\]

where \(D\), \(C\), and \(C_{\text{ss}}\) are the dosage (mg), carbamazepine or clobazam concentration in plasma (μg/mL), and plasma clonazepam concentration at a steady state (μg/mL), respectively and \(K_a\), \(K_e\), \(V_d\), \(t\), and \(CL\) are the elimination rate constant (hr⁻¹), absorption rate constant (hr⁻¹), apparent volume of distribution normalized with bioavailability (L), time from initial administration (hr), and apparent total body clearance normalized with bioavailability (L/hr), respectively. From this point on, the term “clearance” will be used for “apparent total body clearance normalized with bioavailability”. Equation (3) was used for carbamazepine and clobazam, and equation (4) was used for clonazepam.

Results

The pharmacokinetic parameters of phenytoin in CYP2C9*1/*1 were estimated by the Bayesian method, as follows: \(V_{\text{max}} = 3.8\) mg/kg/day and \(K_m = 5.6\) μg/mL. The typical predicted dose of phenytoin was calculated to be approximately 141 mg/day. The percentage of deviation was approxi-
Fig. 1 Profile between serum concentration and dose of phenytoin

Curves A and B were the estimated curves from the subpopulation parameters of CYP2C9*1/*1 with CYP2C19*1/*2 and CYP2C9*1/*3 with CYP2C19*1/*2, respectively, by the Bayesian method. Closed circles (29.8, 29.2 μg/mL) represent serum phenytoin concentrations on July 31 and August 3, below 125 mg/day, respectively. Open circles are the predicted dose of phenytoin.

approximately 11%. The estimated parameters in CYP2C9*1/*3 were also calculated, as follows: $V_{\text{max}} = 3.3 \text{ mg/kg/day}$ and $K_m = 4.1 \text{ μg/mL}$. The typical estimated dose was approximately 129 mg/day. The percentage of deviation was about 3%. Therefore, the predicted dose for CYP2C9*1/*3 better fits the model used [equation (1)] than that for CYP2C9*1/*1 (Fig. 1).

Carbamazepine clearance was altered between 1.7 and 3.4 L/hr, whereas clonazepam clearance was almost unaltered (Fig. 2). Although the carbamazepine dose was decreased by 80%, from 1200 to 1000 mg/day, the plasma concentration increased by 1.2 times when carbamazepine was combined with phenytoin, in the relationship between the daily dose and plasma concentration of carbamazepine. The clearance decreased by 50% based on the alteration. However, clonazepam clearance did not show a remarkable alteration even when clonazepam was combined with carbamazepine and phenytoin.

The alteration of carbamazepine and clobazam clearances and the N-desmethylclobazam/clobazam ratio after re-hospitalization are shown in Table. The carbamazepine and clobazam clearances remained almost unaltered. The N-desmethylclobazam/clobazam ratio was unaltered. The measured value of the urinary 6β-OHF/F ratio was 20.2.

Table Alteration of the N-desmethylclobazam/clobazam ratio and the clearance of clobazam and carbamazepine

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<td>Carbamazepine clearance (L/hr)</td>
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<tr>
<td>Clobazam clearance (L/hr)</td>
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<tr>
<td>Clobazam (μg/mL)</td>
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<tr>
<td>N-desmethylclobazam (μg/mL)</td>
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<td>N-desmethylclobazam/clobazam ratio</td>
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Discussion

1. Discrepancy between the patient’s genotype and phenotype of phenytoin metabolism

The patient was an extensive metabolizer of CYP2C9, which is the main metabolizing enzyme of phenytoin. Her genotype was CYP2C9*1/*1, whereas her phenotype as indicated by the behavior of her serum phenytoin concentration was identical to that of CYP2C9*1/*3. CYP2C9*3 is generally known to be a genetic polymorphism that decreases the enzyme activity. In addition, she had no inhibitor of CYP2C9 in her medications. The reason underlying the discrepancy between her genotype and phenotype of phenytoin metabolism remains an
area of considerable interest. One proposal is that phenytoin as an inducing agent of CYP3A4 might have destroyed the equilibrium of her abnormal heme pathway and depleted CYPs. Her metabolism of phenytoin might have been saturated by the reduction of CYP synthesis.

2. Alteration of the clearance of carba mazepine and clonazepam

The decrease in carbamazepine clearance (Fig. 2) leads us to conjecture that the suppression of CYP biosynthesis was brought on by a mechanism similar to that of the metabolic saturation of phenytoin by the concomitant phenytoin. In addition, an increase in carbamazepine clearance was transiently observed (Fig. 2), which might have been due to a high blood concentration of carbamazepine resulting from the improvement of the equilibrium of CYP biosynthesis, because a month had passed after the discontinuation of phenytoin. The results suggest that phenytoin markedly affected CYP biosynthesis in this patient with porphyria. The influence on CYP might have caused saturation of phenytoin metabolism and an excessive decrease in carbamazepine clearance.

The clonazepam clearance (CL/F) was estimated to be approximately 4.3 L/hr as the mean value (Fig. 2). The total body clearance (CLtot) is calculated to be approximately 4.4 L/hr because the bioavailability of clonazepam is reported to be approximately 0.989. The product of the value of unbound fraction and the hepatic intrinsic clearance was calculated to be 4.4 L/hr from equation (5) when the absorption ratio was regarded to be 1.0 according to the high bioavailability (see “Appendix”). The general value of hepatic blood flow is about 90 L/hr. Therefore, the hepatic extraction ratio of clonazepam was calculated to be approximately 0.05 from equation (7) (see “Appendix”). Clonazepam is considered to be a metabolic capacity-limited agent, according to the calculated value of the hepatic extraction ratio. Carbamazepine is a similar type agent. Carbamazepine clearance seems to be excessively affected by the alteration of hepatic CYP3A4 activity, whereas the clonazepam clearance was not altered in spite of concomitant phenytoin.

The metabolic pathway of clonazepam proceeds by nitroreduction, acetylation, and hydroxylation. The acetylation is reported to be affected by the polymorphic N-acetyltransferase (NAT) that determines the acetylation phenotype of the individual\(^{10}\). This patient was considered to be an intermediate acetylator since her genotype was NAT2*4/*6. There has been no report of a relationship between the NAT2 genotype and a phenotype of clonazepam pharmacokinetics. The influence of the NAT2 genotype on the alteration of clonazepam clearance was unclear.

Seree et al, suggested that the nitroreduction of clonazepam is catalyzed by CYP3A4\(^{11}\). Therefore, clonazepam metabolism might also be affected by the suppression of CYP biosynthesis (Fig. 2). However, the alteration of clonazepam and carbamazepine clearances was different. Binding plasma proteins of phenytoin, clonazepam, and carbamazepine is 90–95%, 80–90%, and 70–80%, respectively\(^{12,13}\). This result implies that the difference in the affinity ratio of binding to plasma proteins affects the alteration of these clearances.

3. Pharmacokinetic evaluation of anticonvulsants after the second hospitalization

The patient’s medication after the second hospitalization was evaluated according to the alteration of carbamazepine clearance, clobazam clearance, and the N-desmethylclobazam/clobazam ratio (Table). The carbamazepine and clobazam clearances and N-desmethylclobazam/clobazam ratio were unaltered after re-hospitalization. However, the measured value of the urinary 6β-OHF/F ratio was slightly high compared with the value (15.4) before the patient left our hospital the first time\(^1\).

Her condition had not improved with a carbamazepine dose of 450 mg/day (see “Case”), whereas the frequency of seizures decreased by increasing the carbamazepine dose to 500 mg/day. Carbamazepine was considered to be effective and safe at a dose of 500 mg/day. The dosage regimen after the second hospitalization was considered to have been appropriately modified as a result.

4. Conclusions

From the pharmacokinetic evaluations for this patient, the following conclusion was established: phenytoin was not a proper medication. Carbamazepine was effective and safe, within a moderate
dose. In addition, the clearance of clonazepam was not affected by carbamazepine. Therefore, the concomitant use of carbamazepine and clonazepam was also considered effective. Clobazam and carbamazepine might be used safely for controlling seizures of porphyria within relatively small doses, at 15 mg/day for the former and at 500 mg/day for the latter.

The influence of anticonvulsants on porphyria was pharmacokinetically evaluated by estimating the clearance of anticonvulsants, in addition to the measurement of urinary 6β-OHF/F. We obtained information on effective and safe medications for porphyria on the basis of estimation of pharmacokinetic parameters.

Acknowledgements

We thank Professor Kenji Matsuyama and Professor Koichi Takahashi of the School of Pharmaceutical Sciences at Mukogawa Women’s University, and Choichiro Miyazaki Ph.D. of Miyazaki Pharmacy.

References

The total body clearance (CL\textsubscript{tot}) for a drug is generally expressed as follows, when a drug is mostly eliminated in the liver:

\[ \text{CL}_{\text{tot}} = f_{\text{ub}} \cdot \text{CL}_{\text{int,h}} / F_a \]  

(5)

where \( F_a \) is the absorption ratio of the drug; \( f_{\text{ub}} \) is the unbound fraction in the blood; and \( \text{CL}_{\text{int,h}} \) is the hepatic intrinsic clearance. Furthermore, the hepatic clearance (CL\textsubscript{h}) and hepatic extraction ratio (ER\textsubscript{h}) of drugs are expressed as follows:

\[ \begin{align*}
\text{CL}_h &= Q_h \cdot f_{\text{ub}} \cdot \text{CL}_{\text{int,h}} / (Q_h + f_{\text{ub}} \cdot \text{CL}_{\text{int,h}}) \\
\text{ER}_h &= f_{\text{ub}} \cdot \text{CL}_{\text{int,h}} / (Q_h + f_{\text{ub}} \cdot \text{CL}_{\text{int,h}})
\end{align*} \]

(6)  

(7)

where \( Q_h \) is the hepatic blood flow; \( f_{\text{ub}} \) is the unbound fraction in the blood; and \( \text{CL}_{\text{int,h}} \) is the hepatic intrinsic clearance. A drug with an ER\textsubscript{h} of more than 0.8 is classified as an agent of the hepatic flow-limited type\textsuperscript{14,15}. A drug with an ER\textsubscript{h} of less than 0.2 is classified as an agent of the metabolic capacity-limited type.

An oral drug absorbed in the gut passes the liver via the portal vein. Only a drug which passes to the liver flows in circulating blood. Therefore, such a drug can be described by the following equation:

\[ \text{AUC}_{\text{po}} = F_h \cdot F_a \cdot \text{AUC}_{\text{iv}} \]  

(8)

where \( F_h \) is the hepatic availability; \( F_a \) is the fraction absorbed into the portal vein from the gut; and AUC\textsubscript{iv} and AUC\textsubscript{po} are the areas under the blood concentration-time curve after intravenous bolus and oral dosing, respectively.

AUC\textsubscript{po} is expressed as a function of dosage (D) and total body clearance after oral dosing (CL\textsubscript{tot,po}) as follows:

\[ \text{AUC}_{\text{po}} = D / \text{CL}_{\text{tot,po}} \]  

(9)

The following equation is obtained from equations (8) and (9):

\[ \text{CL}_{\text{tot,po}} = \text{CL}_{\text{tot,iv}} / (F_h \cdot F_a) \]  

(10)

\( F_h \) is described by the following equation according to the literature\textsuperscript{14,15}:

\[ F_h = Q_h / (Q_h \cdot f_{\text{ub}} \cdot \text{CL}_{\text{int,h}}) \]  

(11)

CL\textsubscript{tot,iv} assumes CL\textsubscript{h} as the hepatic clearance, and equation (5) is obtained from equations (6), (10), and (11).